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Aspirin and Clopidogrel: Lessons from PCI-CLARITY, COMMIT & CHARISMA

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INTRODUCTION

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Platelet activation plays a critical role both in spontaneous coronary artery thrombosis due to atherosclerotic plaque rupture and in thrombotic complications following percutaneous coronary intervention (PCI) with coronary artery stenting. Aspirin use has been shown to safely reduce ischemic events throughout the spectrum of clinical conditions of coronary artery disease (CAD). Therefore, aspirin is part of the standard treatment given to patients with CAD, including those undergoing PCI. Despite the inhibition of cyclooxygenase by aspirin, however, platelet activation can still occur through thromboxane-independent pathways, leading to the aggregation of platelets and the formation of thrombin. For that reason, a more potent antiplatelet effect was sought by using other agents – thienopyridines (ticlopidine, clopidogrel) and glycoprotein IIb/IIIa (GpIIb/IIIa) inhibitors, usually in combination with aspirin. Indeed, depending on the clinical scenario and the concomitant anticoagulants used, regimens combining 2 or more of these antiplatelet agents have resulted in fewer ischemic events and sometimes more bleeding events compared with aspirin alone.

Clopidogrel is an adenosine diphosphate (ADP)-receptor antagonist, a class of oral antiplatelet agents that block the P2Y₁₂ component of the adenosine diphosphate receptor and thus inhibit the activation and aggregation of platelets. It is a potent antiplatelet agent that has a synergistic antithrombotic effect when combined with aspirin. Clopidogrel alone has been shown to benefit patients with documented symptomatic atherosclerosis (recent myocardial infarction [MI], recent stroke, or established peripheral arterial disease). Moreover, clopidogrel added to standard regimen with aspirin further reduces the rate of death and ischemic complications in patients who have undergone PCI, and in those with unstable angina or MI without ST-segment elevation (non-STE ACS). However, the effects of the addition of clopidogrel in patients who have MI with ST-segment elevation (STEMI) and who are receiving or not a standard fibrinolytic regimen, including aspirin, and/or who may undergo PCI remain unclear. The pretreatment with a loading dose and the timing of clopidogrel administration in the setting of the STEMI with or without subsequent PCI also are issues an answer will oblige. In addition, the incremental value of long-term dual antiplatelet therapy, validated in the settings of coronary stenting and non-STE ACS for a mid-term period of 9 to 12 months, is unknown in the broader population of patients with symptomatic or asymptomatic atherothrombosis. PCI-CLARITY [1], COMMIT [2] and CHARISMA [3] are studies that address some of these issues.

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DUAL ANTIPLATELET THERAPY WITH CLOPIDOGREL AND ASPIRIN IN THE SETTING OF STEMI

In patients with STEMI, rupture of an atherosclerotic plaque leads to platelet adhesion, activation, and aggregation, with subsequent vessel occlusion due to thrombus formation. In these circumstances, the most effective pharmacologic reperfusion regimen is concurrent fibrinolytic therapy and platelet inhibition. The marked benefit of such a combination was first established in the Second International Study of Infarct Survival (ISIS-2), in which 35-day mortality among patients with suspected MI was 13.2 percent for those receiving neither streptokinase nor aspirin, approximately 10.5 percent for those given one or the other, and 8.0 percent for those receiving both agents [4]. Subsequently, aspirin serves a foundational role in fibrinolytic therapy regimens.

Although aspirin, administered with or without fibrinolytic therapy, reduces mortality among patients with MI, it has limitations. First, it is a relatively weak antiplatelet agent. It irreversibly inhibits platelet cyclooxygenase, thereby blocking the synthesis of thromboxane A₂, a powerful promoter of platelet activation, but it exerts no effect on thromboxane-independent mediators of platelet activation, such as ADP, thrombin, or serotonin. Second, in up to 30% of persons with coronary artery disease, the condition is relatively resistant or unresponsive to aspirin.

All mediators of platelet activation cause conformational changes in the platelet-surface GpIIb/IIIa receptor, allowing it to bind to circulating fibrinogen and to form platelet-fibrin aggregates. As a result, inhibitors of the GpIIb/IIIa receptor are the most potent antiplatelet agents, since they block the final common pathway for platelet aggregation. In pilot studies, patients who had STEMI who were given aspirin and fibrinolytic therapy had earlier and more complete coronary arterial reperfusion when a GpIIb/IIIa inhibitor was administered concomitantly than when it was not. Subsequently, several trials showed that concomitant administration of reduced-dose fibrinolytic therapy, aspirin, and a GpIIb/IIIa decreased the incidence of in-hospital reinfarction by 1 to 2 percent as compared with full-dose fibrinolytic therapy and aspirin. However, this modest reduction in the incidence of reinfarction was offset by a concomitant increase in the incidence of nonintracranial bleeding. In short, the addition of very potent antiplatelet therapy (in the form of GpIIb/IIIa inhibitors) to fibrinolytic therapy (even at a reduced dose) lessened the risks of reocclusion and recurrent infarction after successful reperfusion, but it did so at the expense of an increase in the frequency of bleeding complications.

PCI in the setting of STEMI has been emerged as a very effective and relatively safe therapy. However, access to such an interventional therapy is not available in most cases. Moreover, the addition of very potent adjunctive antiplatelet

therapy seems to be necessary, and has been shown to benefit patients with ACS who undergo PCI, but it increases the risk of severe hemorrhagic complications.

Clopidogrel is a more potent platelet inhibitor than aspirin, but it is less potent than the GpIIb/IIIa inhibitors. As is the case with aspirin, the response of platelets to clopidogrel is heterogeneous, and resistance to therapy has been reported. In patients with stable angina, dual therapy with aspirin and clopidogrel exerts greater inhibitory effects on platelet activation and aggregation than therapy with either agent alone. In patients with non-STE ACS, an aspirin-clopidogrel combination improved cardiovascular outcomes, as compared with aspirin alone [5,6]. Unfortunately, those treated with combination therapy had a greater risk of bleeding than those treated with aspirin alone, and this finding was particularly noteworthy among those in whom clopidogrel was discontinued within five days before coronary-artery bypass grafting. There was no excess rate of fatal bleeding, bleeding requiring surgical intervention, or hemorrhagic stroke. The excess major bleeding episodes were gastrointestinal hemorrhages and bleeding at the sites of arterial punctures [5].

In conclusion, because many patients are resistant to the effects of a single oral antiplatelet agent, therapy with multiple agents with different mechanisms of action is conceptually attractive, provided that it can be administered without an increased risk of bleeding. The combination of clopidogrel and aspirin has been shown to improve the outcome without any significant increase in the rate of major life-threatening or disabling bleedings in a very wide range of patients with CAD, including those undergoing PCI [5-7]. In contrast, the addition of the very potent GpIIb/IIIa inhibitors to the standard regimen including aspirin improves the outcome too, but increases the risk for major bleeding complications. Therefore, the combination of clopidogrel and aspirin should be investigated in the setting of management of patients with STEMI.

THE PCI-CLARITY STUDY

On March 2005, the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)-Thrombolysis in Myocardial Infarction (TIMI) 28 investigators reported their findings from 3491 STEMI patients receiving fibrinolytic therapy, including aspirin, who were randomized to receive a 300-mg loading dose and then a 75-mg daily dose of clopidogrel or placebo [8]. Patients were enrolled mainly in Western Europe and North America. The average time from symptom onset to fibrinolytic administration was just under 3 h and more than two-thirds of patients received a fibrin-specific lytic, with the rest receiving streptokinase. Patients underwent coronary angiography 2–8 days after the start of study medication (median of 3.5 days). Of these patients, 57.2% from the clopidogrel

group and 56.6% from the placebo group underwent PCI during the index hospitalization and formed the basis for PCI-CLARITY [1]. The decision to perform PCI was at the operator's direction. Moreover, all patients undergoing coronary stent placement received an open-label 300-mg loading dose of clopidogrel after the initial angiogram, followed by a daily dose of 75 mg. The primary endpoint was an occluded infarct-related artery or death or MI before angiography, and patients were also followed for 30 days for clinical events. The CLARITY-TIMI 28 study demonstrated the benefit of adding clopidogrel to aspirin and fibrinolytic therapy for STEMI. The treatment improved the patency rate of the infarct-related artery and reduced the odds of the composite primary efficacy end point of an occluded infarct-related artery or death or recurrent MI by the time of angiography, a median of 3.5 days after enrollment. Moreover, by 30 days, the treatment led to a significant reduction in the ischemic complications. The study was not specifically powered to assess individual clinical end points at 30 days, but cardiac mortality rates appeared similar between the clopidogrel and placebo groups (4.4% vs. 4.5%), even though the rate of reinfarction was lower with clopidogrel (4.1% vs. 5.9%; OR, 0.69; $P = 0.02$). The respective rates of major bleeding complications were similar between the 2 groups (1.9% vs. 1.7%). Weighing the observations from the CLARITY-TIMI 28 and abciximab-STEMI meta-analysis [9], it can be concluded that the addition of either abciximab or clopidogrel to the aspirin component of thrombolytic therapy reduces the 30-day occurrence of reinfarction by roughly one-third but does not affect mortality. In these studies, the addition of abciximab significantly increased major bleeding complications while the addition of clopidogrel does not [8,9]. However, in the most recent ISAR-REACT 2 trial, a triple antiplatelet therapy (clopidogrel, including loading dose of 600 mg, aspirin, abciximab) in patients undergoing PCI did not significantly increase the risk of major and minor bleeding as well as need for transfusion [10].

Clopidogrel also has a well-established record of reducing ischemic events without increasing bleeding complications when used for PCI. Unlike intravenously administered GpIIb/IIIa inhibitors, which are effective in minutes, clopidogrel requires hours to days after oral administration to become effective, according to the initial dose. Several post-hoc analyses from large-scale PCI trials showed patients receiving clopidogrel hours to days before, rather than at the time of PCI, experienced substantially fewer periprocedural ischemic events. The first prospective study of clopidogrel pretreatment, CREDO [7], randomized 2,116 patients to 300-mg pretreatment versus no pretreatment and observed that clopidogrel at this loading dose needed to be given at least 15 hours prior to PCI to be significantly effective and 24 hours preprocedure to be maximally effective. For patients scheduled in advance for cardiac catheterization and possible PCI, pretreatment with clopidogrel at least a day before the procedure became

intuitive. On the other hand, because the biological effect of clopidogrel lasts for days, many physicians have been reluctant to pretreat patients until coronary angiography has excluded their need for surgical revascularization. This concern was borne out in the CURE trial [5], in which patients with ACS randomized to receive clopidogrel and undergoing surgical revascularization within 5 days of receiving clopidogrel had a 53% increased risk for major bleeding compared with similar patients receiving placebo.

PCI-CLARITY [1] study addressed several important issues regarding clopidogrel pretreatment before PCI among STEMI patients. It was a prespecified test of the hypothesis that in patients undergoing PCI after initial pharmacological therapy for STEMI, clopidogrel pretreatment hours to days before PCI is superior to clopidogrel treatment initiated at the time of PCI in preventing major adverse cardiovascular events. The study demonstrated a substantial reduction in the composite end point of cardiovascular death, reinfarction, or stroke from PCI to 30 days among those pretreated with clopidogrel (3.6% vs. 6.2%; OR, 0.54 [95% CI, 0.35-0.85]; $P = 0.008$). In addition, clopidogrel pretreatment was associated with a reduced odds of reinfarction or stroke prior to PCI (4.0% vs. 6.2%; OR, 0.62 [95% CI, 0.40-0.95]; $P = 0.03$). This benefit was seen in patients with STEMI treated with fibrinolysis who subsequently underwent PCI on average 3 days later, but with a consistent benefit regardless of the time from initiation of pretreatment to PCI. Moreover, benefits were seen regardless of whether patients received a GpIIb/IIIa inhibitor at the time of PCI or whether patients received a loading dose of open-label clopidogrel at the time of PCI. Major bleeding events occurred at a similar frequency between the groups (0.5% vs. 1.1%, respectively; $P = 0.21$). In conclusion, clopidogrel pretreatment significantly reduces the incidence of cardiovascular death or ischemic complications both before and after PCI and without a significant increase in major or minor bleeding. These data add further support to the early use of clopidogrel in STEMI and the strategy of routine clopidogrel pretreatment in patients undergoing PCI.

Several points from CLARITY and PCI-CLARITY are worthy of mention. First, few patients presenting with STEMI undergo a CABG surgery during the index hospitalization, so little concern should be given regarding early clopidogrel administration and the subsequent need for urgent surgery (only 6% of patients in CLARITY underwent CABG surgery). Second, patients who undergo PCI in the setting of an ACS (non-STEMI and STEMI) are at particularly high risk for periprocedural MI. As such, it is not surprising that the relative risk reduction in ischemic events provided by clopidogrel was twice as high among CLARITY patients who underwent PCI than those who did not. Specifically, patients receiving clopidogrel pretreatment before angiography and who were treated medically or underwent CABG surgery had approximately a 17% risk reduction for reinfarction at 30 days (2.0%

vs. 2.4%) compared with a 35% reduction among similarly treated patients who underwent PCI (5.9% vs. 8.9%). In PCI-CLARITY, roughly two thirds of the reinfarctions occurred in the 3.1 days (median) before PCI, with the remainder occurring during or soon after revascularization. Importantly, clopidogrel treatment provided a consistent level of protection against reinfarction during both of these intervals (OR, 0.60). A similar bimodal occurrence of events and protection has been observed among non-STEMI ACS patients treated before and during PCI with GpIIb/IIIa inhibitors.

A third important point concerns the remaining uncertainty about the optimal dose and timing of clopidogrel administration. The 300-mg loading dose used in CLARITY is established to be effective in the PCI-CURE and CREDO [7] trials, yet other studies suggest the 300-mg loading dose is incompletely effective or requires a longer minimum interval for peak effect than noted in PCI-CLARITY. ARMYDA-2 study showed that a 600-mg loading dose of clopidogrel 4 to 8 hours before PCI safely and more effectively reduced the occurrence of periprocedural infarctions than a 300-mg loading dose. Yet, even the 600-mg dose may not be optimal, as suggested by data from the recently presented ALBION trial, in which a 900-mg loading dose provided an even greater and more rapid antiplatelet effect than 600 mg as determined by several *ex vivo* measure of platelet function. Patients receiving long-term clopidogrel therapy may also benefit from an additional loading dose. Indeed, a recent study demonstrated that a 600-mg loading dose of clopidogrel given to patients already receiving long-term (>1 month) clopidogrel therapy was able to achieve additional aggregation inhibition beyond that provided by the daily dose. The PCI-CLARITY study provided an opportunity to assess some of these concepts clinically since it was recommended that all patients undergoing coronary stent placement receive an open-label 300-mg loading dose of clopidogrel after the initial angiogram. Patients who were randomized to receive a 300-mg loading dose and then a 75-mg daily dose of clopidogrel at enrollment (pretreatment) and who subsequently received an additional 300-mg dose at the time of PCI (retreatment) had the lowest rate of death, reinfarction, and stroke following PCI to 30-day follow-up compared with those who received a clopidogrel loading dose only at enrollment, only during PCI, or at neither time.

The PCI-CURE [6] and CREDO [7] provided important data on the value of clopidogrel pretreatment in patients with non-STE ACS undergoing PCI and in patients undergoing planned, elective PCI, respectively. The PCI-CLARITY study builds on these prior studies in several important ways. First, PCI-CLARITY studied patients with STEMI and showed a benefit with clopidogrel pretreatment in these patients who are at the highest risk for early recurrent ischemic events. Clopidogrel thus appears to be an important component to include in a pharmacoinvasive approach to patients with STEMI. Second, this study evaluated a broad range of durations of pretreatment

from less than 6 hours to 8 days and showed a consistent benefit of clopidogrel pretreatment across this range of pretreatment durations. Of note, although the maximal effect of clopidogrel on platelet inhibition may not occur until 6 or more hours after a 300-mg loading dose, some degree of platelet inhibition can be measured as early as 90 minutes. Prior studies have shown that the degree of platelet inhibition at the time of PCI is strongly related to the likelihood of major adverse cardiovascular events following PCI. PCI-CLARITY suggests that in the setting of an ACS with heightened platelet activation and PCI causing immediate and further platelet activation, even relatively brief durations of pretreatment with clopidogrel before PCI may translate into improved patient outcomes. Third, PCI-CLARITY showed a benefit with clopidogrel pretreatment regardless of whether a standard loading dose of clopidogrel was administered in the cardiac catheterization laboratory at the time of PCI. Fourth, the study showed a benefit with clopidogrel pretreatment regardless of GpIIb/IIIa inhibitor use peri-PCI in patients with ACS. This finding is supported by results from nonrandomized comparisons in registries and in the TARGET and REPLACE trials, and builds on a similar observation made in the setting of elective PCI in CREDO [7] and non-STE ACS in PCI-CURE.

Taken together, the PCI-CURE, CREDO, and PCI-CLARITY, demonstrate a clear and consistent benefit with clopidogrel pretreatment for PCI across the spectrum from stable coronary artery disease to STEMI, and regardless of patient demographics or the use of a GpIIb/IIIa inhibitor at the time of PCI. The significant reduction in adverse cardiovascular events before PCI suggests that a strategy of clopidogrel pretreatment should be initiated as soon as possible. Accordingly, even if clopidogrel is not given at presentation, once the decision is made to proceed with angiography, and hence possible PCI, initiation of pretreatment will maximize the benefit.

In the PCI-CLARITY study, like in PCI-CURE, the event curves following PCI continued to diverge over time despite almost all patients in both treatment groups receiving open-label clopidogrel following PCI. This observation suggests that the beneficial effect of clopidogrel may extend beyond just prevention of platelet aggregation and myocyte necrosis during the procedure. By blocking the P2Y₁₂ receptor, clopidogrel inhibits platelet activation and thus may have more widespread effects on endothelial cells, leukocytes, and inflammation. For example, clopidogrel has been shown to blunt expression of both P-selectin and CD40 ligand, the former of which contributes to platelet-leukocyte aggregation and the latter of which can trigger an inflammatory response in endothelial cells. In addition, thienopyridine pretreatment has been shown to attenuate the rise in CRP immediately after PCI and to decrease the need for target vessel revascularization over 1 year.

Finally, like any study, PCI-CLARITY has limitations,

particularly since PCI was not randomized. The trial excluded many patient groups known to be at particularly high risk for death, reinfarction, or major bleeding events such as patients older than 75 years, those with prior CABG surgery, prior intracranial hemorrhage or non-hemorrhagic stroke, or with a creatinine level higher than 2.5 mg/dL (221 μ mol/L). While the investigators carefully performed propensity analysis to correct for selection bias for undergoing PCI, it is possible that residual confounding factors were present. For example, undiscovered factors may exist that explain why patients receiving a GpIIb/IIIa inhibitor had event rates higher than patients not receiving GpIIb/IIIa inhibitors or why one fourth of patients did not receive open-label clopidogrel loading at the time of PCI. However, despite the existing limitations, PCI-CLARITY provides important data, and application of the study findings seems straightforward — patients receiving thrombolytic therapy for STEMI should also receive a 300-mg loading dose of clopidogrel followed by 75 mg daily. Additionally, clinicians should consider giving 600 mg of clopidogrel as a loading dose, even though this approach has not been formally tested with thrombolytic therapy. So far, no major safety concerns have emerged with 600- or 900-mg loading doses. Finally, all patients not receiving a loading dose within several days of angiography should be considered for clopidogrel retreatment (i.e., repeat loading dose) at the time of PCI.

In conclusion, PCI-CLARITY found that in high-risk patients with STEMI treated with fibrinolytic therapy, a strategy of clopidogrel pretreatment significantly reduced the incidence of cardiovascular death and ischemic complications both before and after PCI without a significant increase in major or minor bleeding. These data add further support to the early use of clopidogrel in STEMI and the broader strategy of clopidogrel pretreatment in patients undergoing PCI.

THE COMMIT STUDY

Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) [2] is the second of the two trials published last year that defined the role of combined regimen of clopidogrel and aspirin in the setting of STEMI [2,8]. COMMIT addressed the net effects on mortality and major morbidity of adding clopidogrel to aspirin in this setting. The study enrolled nearly 46,000 patients who presented within 24 hours after the onset of a suspected acute MI and were randomly assigned to receive clopidogrel (75 mg daily) or placebo in addition to aspirin. Treatment was to continue until discharge or up to 4 weeks in hospital (mean 15 days in survivors). There were several differences between COMMIT and the above mentioned CLARITY-TIMI 28. COMMIT was done exclusively in China, there was no upper age limit (26% of patients aged 70 years or older), and the average time from symptom onset to presentation was a little over 10 hours. Only half of patients

received fibrinolytic therapy on presentation (urokinase), and clopidogrel was administered as 75 mg daily, without a loading dose. Fewer than 5% of patients went on to have PCI. The two prespecified co-primary outcomes were: (1) the combination of death, reinfarction, or stroke; and (2) death from any cause during the scheduled treatment period. In short, this large randomized trial showed that addition of clopidogrel to aspirin reduces mortality and major morbidity in a wide range of patients with suspected acute MI, and these benefits seem to be largely independent of, and hence additional to, those of other standard treatments such as fibrinolytic and anticoagulant therapy. The findings also show that such treatment is safe, with no apparent increase in life-threatening bleedings even when given with fibrinolytic therapy, or to older patients.

Several points from COMMIT are worth highlighting. To begin, a fascinating and unexpected observation was that the benefit of clopidogrel had emerged as early as the first day after a simple first dose of 75 mg without an initial loading dose. Indeed, some of the clinical benefit of clopidogrel seemed to emerge rapidly, with a marginally significant 12% (SE 6; $P = 0.05$) proportional reduction in death, reinfarction, or stroke on day 0 (i.e., within an average of 12 hours of starting treatment) and a somewhat more significant 11% (99% CI 0–20%, $P = 0.01$) benefit when the results on days 0 and 1 were combined. Although it generally takes several days rather than hours for clopidogrel to reach steady-state antiplatelet effects without an initial loading dose, partial antiplatelet effects do emerge within a few hours after administering 75 mg clopidogrel orally. One may speculate that even such modest degrees of platelet inhibition translate into a clinical benefit in the critical setting of acute MI or that the clinical benefit was in a subset of clopidogrel hyper-responders. The addition of an initial loading dose of clopidogrel could, however, produce more rapid antithrombotic effects. Indeed, in the CLARITY-TIMI 28 trial among 3,491 STEMI patients given fibrinolytic therapy plus aspirin, a 300-mg loading dose of clopidogrel, followed then by 75 mg once daily, was associated with a significant reduction in the rate of the composite end point of an occluded infarct-related artery on angiography or death or MI before angiography (reduction by 31%, $P < 0.001$), and improved all angiographic measurements at a median of 3.5 days. Specifically, this treatment with clopidogrel decreased the rate of finding an occluded infarct-related artery (41% reduction in the odds, $P < 0.001$) and the rate of recurrent MI (30% reduction in the odds, $P = 0.08$), and increased the odds of achieving optimal epicardial flow by 36% ($P < 0.001$) and the odds of achieving optimal myocardial reperfusion by 21% ($P = 0.008$). Likewise, in the CURE trial among 12,562 patients with non-STE ACS given aspirin, an initial 300 mg loading dose of clopidogrel was associated with a 20% proportional reduction in the risk of major vascular events within 24 hours of the initiation of treatment, although this early trend was also not significant. Even higher loading doses of

clopidogrel could produce even greater antiplatelet effects more rapidly, although the bleeding risk would need to be monitored, especially in older patients who are at somewhat greater risk of bleeding, but also at somewhat greater risk of an occlusive vascular event.

A second important point concerns the remaining uncertainty about the net effect on mortality of adding clopidogrel to aspirin. Previous studies, such as the CURE in patients with non-STE ACS and the CLARITY-TIMI 28 in patients with STEMI, showed a significant reduction in the rate of the composite end point or in the rate of recurrent ischemia or reinfarction but failed to show any clear reduction in the rate of death from cardiovascular causes. Specifically, CLARITY-TIMI 28 showed that clopidogrel had the greatest effect on the rate of an occluded infarct-related artery (reducing it from 18.4 percent to 11.7 percent; 41% reduction in the odds; $P < 0.001$), but it had no significant effect on the rate of death from any cause. However, these studies were not powered to detect a survival benefit. In COMMIT, clopidogrel significantly reduced the odds of the composite of death, MI, or stroke, and, perhaps most impressively, mortality alone. These data show the first change in pharmacological reperfusion therapy for STEMI in over a decade to achieve a mortality benefit. Although fibrinolytics help open an occluded artery, reocclusion remains a significant problem. The additive antiplatelet effect of clopidogrel on top of aspirin may help shift the balance in favour of sustained reperfusion rather than reocclusion. One may speculate that such a preservation of the patency could have led to the translation of the angiographic benefit into an immediate reduction in mortality. Results from CLARITY-TIMI 28 and COMMIT together provide additional validation of the open-artery hypothesis.

Finally, it is reassuring that there was no excess in either major bleeding or intracranial hemorrhage in either COMMIT or CLARITY-TIMI 28, by contrast with other attempts to improve reperfusion in acute MI such as the GUSTO V trial. However, it must be noted that there are safety data on clopidogrel in the elderly receiving lytic therapy only in the absence of a loading dose.

In terms of implications of COMMIT for clinical practice, adding clopidogrel 75 mg daily over a standard therapy for acute STEMI including aspirin, approximately 10 deaths, reinfarctions, or strokes would be prevented for every 1000 patients treated for 2 weeks. Moreover, daily aspirin prevents another 40 deaths, nonfatal reinfarctions, or strokes per 1000 patients with suspected acute STEMI treated for one at least month, with these early benefits persisting for at least 10 years. Consequently, compared with no antiplatelet treatment, it can be inferred that the combination of clopidogrel plus aspirin prevents an average of about 50 major vascular events per 1000 treated for just a few weeks soon after the onset of acute MI. However, a more rapid and more potent antiplatelet therapy with a loading dose of clopidogrel, the use of a fibrin-specific

fibrinolytic agent instead of the non-specific urokinase, and a more prolonged use of the combined antiplatelet regimen after acute MI would produce even greater absolute benefits.

In summary, building on the background of aspirin, dual antiplatelet therapy, now with the addition of clopidogrel to aspirin, represents a major advance in the care of patients with acute STEMI, with clear benefit across a broad range of patient demographics and practice patterns.

LONG-TERM DUAL ANTIPLATELET THERAPY WITH CLOPIDOGREL AND ASPIRIN

Platelets have been shown to play a central role in the pathogenesis of atherothrombotic process. Low-dose aspirin has been shown to reduce ischemic outcomes in patients above a certain risk threshold. Therefore, antiplatelet therapy with aspirin has earned its rightful place as a cornerstone of treatment for reducing cardiovascular events in patients with established vascular disease. However, aspirin alone in many instances is not sufficient to prevent ischemic events in patients at high risk, because it inhibits only the cyclooxygenase pathway, leaving other powerful thromboxane-independent mediators of platelet activation unaffected, and because in up to 30% of persons, the condition is relatively resistant or unresponsive to aspirin. Clopidogrel, an ADP P2Y₁₂-receptor antagonist, is another potent antiplatelet agent. As monotherapy, clopidogrel has been shown to be superior to aspirin alone in reducing the risk of ischemic stroke, MI, or death from vascular causes in patients with established vascular disease [11]. However, there is debate as to whether P2Y₁₂-receptor blockade provide uniform benefit among patients with vascular disease. For that reason, a more consistent and potent antiplatelet effect was sought. Thereafter, dual antiplatelet therapy with clopidogrel plus aspirin has been found to be superior to monotherapy with either drug alone. Since CAPRIE [11], four large clinical trials have added to the body of evidence that supports the use of dual antiplatelet therapy in patients with ACS and in those undergoing PCI [2,5,7,8]. However, these studies were limited into the setting of symptomatic CAD, which represents only a part of the entire burden of the atherosclerotic vascular disease. Furthermore, the value of dual antiplatelet therapy has been evaluated only for a very short- up to a mid-term period of 9 to 12 months. Accordingly, the logical next step was the evaluation of the potential role of the long-term dual antiplatelet therapy in a broad population of patients with established vascular disease (documented history of established CAD, cerebrovascular disease, or peripheral arterial disease) or multiple cardiovascular risk factors.

The Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, a prospective, multicenter, random-

ized, double-blind, placebo-controlled study, tested the hypothesis that long-term treatment with a combination of clopidogrel plus aspirin may provide greater protection against cardiovascular events than aspirin alone in a broad population of patients at high risk [3]. Therefore, the trial was probing uncharted territory in determining whether long-term dual antiplatelet therapy would be of incremental clinical value in patients with vascular disease without an acute manifestation of injury. The study enrolled 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin and followed them for a median of 28 months. The primary efficacy end point was a composite of MI, stroke, or death from cardiovascular causes.

As regards the whole study population, there was no significant benefit associated with clopidogrel plus aspirin as compared with placebo plus aspirin in reducing the incidence of the primary end point of MI, stroke, or death from cardiovascular causes (6.8% vs. 7.3%, $P = 0.22$). There was a moderate, though significant, benefit in reducing the secondary composite end point of MI, stroke, death from cardiovascular causes, or hospitalization for unstable angina, transient ischemic attack, or revascularization (16.7% vs. 17.9%, absolute reduction 1.2%; $P = 0.04$). This finding was mainly due to the significant reduction of the hospitalizations (11.1% vs. 12.3%, absolute reduction 1.2%; $P = 0.02$). The rate of severe bleeding was not significantly greater with clopidogrel than with placebo, but a trend prompting concern was noted (1.7% vs. 1.3%; $P = 0.09$), and clopidogrel was associated with a significant increase in the rate of moderate bleeding (2.1% vs. 1.3%, $P < 0.001$). A total of 94 secondary ischemic end points (mainly hospitalizations) were prevented with clopidogrel, at a cost of 93 moderate or severe bleeding events.

A subgroup analysis suggested that clopidogrel was beneficial with respect to the primary efficacy end point in patients who were classified as symptomatic (6.9% vs. 7.9%, $P = 0.046$). However, this observation should be interpreted with caution, but not just because the interaction term was only marginally significant and not adjusted for multiple analyses. Moreover, it must be noted that the characteristics that differentiate patients in this subgroup are not sufficiently distinct. As reported, some of the patients termed “asymptomatic” had major cardiovascular events, and one would assume that a large proportion of the patients termed “symptomatic” also had multiple risk factors. Clopidogrel had no significant effect on death from cardiovascular causes in this subgroup. As regards the bleedings, the risk of moderate or severe bleeding in symptomatic patients was greater with clopidogrel than with placebo, although there was no significant increase in intracranial or fatal bleeding.

On the other hand, the risk associated with dual antiplatelet therapy in the asymptomatic group (only multiple

cardiovascular risk factors) was not anticipated. Although the difference in the rates of primary end point between clopidogrel and placebo was not significant (6.6% vs. 5.5%, $P = 0.20$), there were excess fatalities and a heightened risk of bleeding complications in this group. There was a significant increase in the rate of death from all causes among the patients assigned to clopidogrel plus aspirin as compared with those assigned to placebo plus aspirin (5.4% vs. 3.8%, $P = 0.04$) as well as an increase in the rate of death from cardiovascular causes among those assigned to clopidogrel (3.9% vs. 2.2%, respectively; $P = 0.01$). There is no reasonable and convincing interpretation of this unexpected finding, at present. It is possible that established vascular disease represents a crude proxy for hyperactive platelets. If this concept is accepted, dual antiplatelet therapy would be anticipated to be associated with greater efficacy and a lower rate of bleeding in the subgroup of symptomatic patients. However, reduced basal platelet activity in asymptomatic patients would be expected to be a liability, increasing the risk of bleeding complications, including possible hemorrhage into an arterial plaque. Whatever the explanation, it appears that until proven otherwise, clinicians should avoid dual antiplatelet therapy in patients without established vascular disease. Moreover, the issue of whether dual antiplatelet therapy is beneficial in more specific subgroups of the population of patients with atherothrombotic disease or risk will require further study.

In terms of hemorrhagic complications in the subgroup analysis, there were no significant differences in the rates of severe bleeding between clopidogrel and placebo both among symptomatic (1.6% vs. 1.4%, $P = 0.39$) and among asymptomatic patients (2.0% vs. 1.2%, $P = 0.07$), but a noticeable trend in favor of placebo was observed in both subgroups. Likewise, the rate of moderate bleeding among asymptomatic patients tended to be greater with clopidogrel than with placebo, but the difference was not significant (2.2% vs. 1.4%, $P = 0.08$). In contrast, in the symptomatic group, there was a significant increase in the rate of moderate bleeding among patients assigned to clopidogrel as compared with those assigned to placebo (2.1% vs. 1.3%, $P < 0.001$).

In conclusion, the combination of clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes among patients with stable cardiovascular disease or multiple cardiovascular risk factors. Furthermore, the risk of moderate-to-severe bleeding was increased. CHARISMA trial does not support the use of dual antiplatelet therapy across the broad population tested. There was a potential benefit in symptomatic patients (those with established vascular disease); this finding requires further study. Data on mortality rates suggest that dual antiplatelet therapy should not be used in patients without a history of established vascular disease.

SUMMARY

PCI-CLARITY [1] and COMMIT [2] addressed the role of adding clopidogrel to the standard regimen for acute STEMI including aspirin. The PCI-CLARITY study was a prospectively planned analysis of the 1863 patients undergoing PCI after mandated angiography in CLARITY-TIMI 28, a randomized, double-blind, placebo-controlled trial of clopidogrel in patients receiving fibrinolytics for STEMI. Patients received aspirin and were randomized to receive either clopidogrel (300-mg loading dose followed by 75 mg once daily) or placebo initiated with fibrinolysis and given until coronary angiography, which was performed 2 to 8 days (median, 3.5 days) after initiation of the study drug. For patients undergoing coronary artery stenting, it was recommended that open-label clopidogrel (including a loading dose) be administered after the diagnostic angiogram. It must be noted that all PCI-CLARITY patients received fibrinolytics and aspirin, approximately 50% of them randomized to receive clopidogrel and 50% to receive placebo from the time of initial presentation until angiography, and nearly all of them received an open-label clopidogrel (including a loading dose) after angiography and underwent coronary stenting. In addition, patients were enrolled mainly in Western Europe and North America, and the upper age limit was 75 years. This study addressed the hypothesis that in patients undergoing PCI after initial pharmacological therapy for STEMI, clopidogrel pretreatment hours to days before PCI is superior to Clopidogrel treatment initiated at the time of PCI in preventing major adverse cardiovascular events.

The COMMIT trial enrolled nearly 46,000 patients who presented within 24 hours after the onset of a suspected acute MI and were randomly assigned to receive clopidogrel (75 mg daily) or placebo in addition to aspirin. Treatment was to continue until discharge or up to 4 weeks in hospital (mean 15 days in survivors). The study was done exclusively in China, there was no upper age limit (26% of patients aged 70 years or older), and the average time from symptom onset to presentation was a little over 10 hours. Only half of patients received fibrinolytic therapy on presentation (urokinase), and clopidogrel was administered as 75 mg daily, without a loading dose. Fewer than 5% of patients went on to have PCI. COMMIT addressed the net effects on mortality and major morbidity of adding clopidogrel to aspirin in the setting of STEMI.

Despite differences regarding the design, setting and participants in the PCI-CLARITY and COMMIT, both trials concluded that clopidogrel effectively reduces the incidence of major adverse cardiovascular events without a significant increase in major or minor bleeding. These effects were consistent across a very wide range of patient subgroups and independent of other pharmacological or interventional treatments being used. Surprisingly, some of the clinical ben-

efit of clopidogrel does emerge rapidly within a few hours after administering even a single dose as low as 75 mg orally, although loading doses of ≥ 300 could produce even greater antiplatelet effects more rapidly. Indeed, in the COMMIT trial, clopidogrel 75 mg once daily reduced the rate of death, reinfarction, or stroke by 12% within the first 12 hours ($P = 0.05$), by 11% within the first day ($P = 0.01$), and by 9% ($P = 0.002$) among patients treated for 2 weeks; while in the PCI-CLARITY trial, pretreatment with clopidogrel (300-mg loading dose followed by 75 mg once daily) reduced the rate of reinfarction or stroke over a median 3.5-day period prior to PCI by 35% ($P = 0.03$), and the incidence of cardiovascular death, reinfarction, or stroke from PCI through 30 days by 42% ($P = 0.008$). As regards the effect on mortality, a clopidogrel treatment, even as 75 mg once daily, initiated at the time of presentation seems to reduce the short-term mortality after acute STEMI regardless of other treatments [2]; and the clopidogrel pretreatment hours to days before PCI strongly trends to reduce the incidence of cardiovascular death after elective PCI for STEMI initially treated with fibrinolytics and aspirin [1].

Accordingly, these data add further support to the early use of clopidogrel in STEMI and to the broader strategy of clopidogrel pretreatment in patients undergoing to PCI.

The CHARISMA [3] trial tested the hypothesis that long-term treatment with a combination of clopidogrel plus aspirin may provide greater protection against cardiovascular events than aspirin alone in a broad population of patients at high risk. This study enrolled nearly 15,600 patients with either clinically evident cardiovascular disease or multiple risk factors. These patients were randomly assigned to receive clopidogrel (75 mg per day) plus low-dose aspirin (75 to 162 mg per day) or placebo plus low-dose aspirin and were followed for a median of 28 months. The primary efficacy end point was a composite of MI, stroke, or death from cardiovascular causes. The secondary efficacy end point was a composite of primary, or hospitalization for unstable angina, transient ischemic attack, or revascularization.

As regards the whole study population of patients with stable cardiovascular disease or multiple cardiovascular risk factors, the combination of clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of the primary efficacy end point. There was a moderate, though significant, reduction in the secondary composite end point (absolute reduction 1.2%, relative reduction by 6.7%; $P = 0.04$), but it mainly was due to the reduction of hospitalizations (absolute reduction 1.2%, relative reduction by 10; $P = 0.02$). Moreover, a strong trend prompting concern was noted regarding severe bleeding (increase by 30%, $P = 0.09$), and the rate of moderate bleeding was significantly greater with clopidogrel than with placebo. Finally, a total of 94 secondary ischemic end points (mainly hospitalizations) were prevented with clopidogrel, at a cost of 93 moderate or severe bleeding

events.

As regards the subpopulation of patients with symptomatic but stable atherosclerotic disease, clopidogrel was associated with a marginally significant increase in the rate of primary efficacy end point, but it had no effect on death from cardiovascular causes. Moreover, clopidogrel increased the risk of moderate or severe bleeding in this subgroup, although there was no significant increase in intracranial or fatal bleeding.

On the other hand, long-term dual antiplatelet therapy in the subpopulation of asymptomatic patients with multiple cardiovascular risk factors was associated with surprisingly unexpected results. Although the difference by 20% in the rates of primary end point between clopidogrel and placebo was not significant, there were excess fatalities and a heightened risk of bleeding. Specifically, clopidogrel use was associated with a significant increase in the rate of death from all causes (nearly by 30%, $P = 0.04$) as well as in the rate of death from cardiovascular causes (by 44%, $P = 0.01$). At present, there is no reasonable and convincing interpretation of this unexpected finding.

In conclusion, the combination of clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular causes among patients with stable cardiovascular disease or multiple cardiovascular risk factors. Furthermore, the risk of moderate-to-severe bleeding was increased. CHARISMA trial does not support the use of dual antiplatelet therapy across the broad population tested. There was a potential benefit in symptomatic patients with established vascular disease. However, whether dual antiplatelet therapy is beneficial in more specific subgroups of the population of patients with atherothrombotic disease or risk requires further study. Moreover, data on mortality rates suggest that dual antiplatelet therapy should not be used in patients without a history of established vascular disease. So far, the incremental value of long-term dual antiplatelet therapy has been validated only in the settings of coronary stenting and non-STE ACS for a mid-term period up to 9 to 12 months. If anything, a subgroup analysis could be used to generate a hypothesis for future studies to help define the currently blurry distinction between the benefits and risks of dual antiplatelet therapy in patients with acute injury and those in patients with more stable vascular disease.

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